ORIGINAL ARTICLE

THE COGNITIVE FUNCTION OF ANTHRACYCLINE-BASED ADJUVANT CHEMOTHERAPY IN WOMEN WITH BREAST CARCINOMA

Sukendro Sendjaja[1], Ibnu Purwanto[2], Johan Kurnianda[2*]

1. Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta
2.Subdivision of Hematology Oncology Medic, Department of Internal Medicine, Dr. Sardjito General Hospital, Yogyakarta

**Corresponding Author: jkurnianda@yahoo.com*

ABSTRACT

***Objective**: The objective of this study was to determine the changes in cognitive function of anthracycline-based adjuvant chemotherapy in women with breast carcinoma.*

***Method**: The study design was prospective longitudinal study. The breast cancer patients who received anthracycline-based adjuvant chemotherapy were recruited from Internal Medicine Department wards and TULIP cancer outpatient clinic Sardjito General Hospital Yogyakarta. Subjects eligible with inclusion and exclusion criteria were examined for cognitive function by mini-mental state examination (MMSE) before chemotherapy (T_0) at 3 weeks after 2nd adjuvant chemotherapy (T_1), 3 weeks after 4th adjuvant chemotherapy (T_2), and 3 months after 4th adjuvant chemotherapy (T_3). The mean difference of MMSE scores were analyzed with Wilcoxon-signed rank test and $P<0.05$ was considered statistically significant.*

***Result**. There were 47 subjects eligible to study criteria in October 1st 2008 – October 31st 2009. Forty subjects finished this study and were analyzed. The mean age was 47.08±6.65 with age ranged from 27 to 61 years old. The mean MMSE scores before chemotherapy (T_0), 3 weeks after 2nd adjuvant chemotherapy (T_1), 3 weeks after 4th adjuvant chemotherapy (T_2), and 3 months after 4th adjuvant chemotherapy (T_3) were 29.28±1.20, 28.60±1.69, 28.18±1.89, and 27.85±2.03, respectively. The mean MMSE score changes (ΔT_0-T_1), (ΔT_0-T_2), and (ΔT_0-T_3) were 0.68±0.80, 1.10±1.06, and 1.43±1.36, respectively and $P<0.001$. The incidence of cognitive impairment with MMSE scores < 24 was 2.5% and $P=1.0$.*

***Conclusion**: There was a significant decline of MMSE score in women with breast carcinoma who received anthracycline-based adjuvant chemotherapy at 3 weeks after 2nd adjuvant chemotherapy, 3 weeks after 4th adjuvant chemotherapy, and 3 months after 4th adjuvant chemotherapy compared with prior to chemotherapy.*

***Key Words:** Cognitive Function, Breast Cancer, Adjuvant Chemotherapy, Anthracycline*

INTRODUCTION

Breast Cancer is the most common cancer in women. In US, 20-24 years old women had lowest incidence of breast cancer. In 2000-2004, 1.4 cases per 100.000 women, and 75-79 years old women had the highest incidence reaching 464.8 cases per 100.000 women[1]. Cancer incidence in Indonesia has not well known yet due to unavailable registration data. Data from Globocan, an International Agency for Research on Cancer (IARC) in 2002, and estimated breast cancer incidence in Indonesia is 26 per 100.000 women. Breast cancer is the second most leading cancer in Indonesia after cervical cancer on pathological-based study, with relative frequency 15.83% after cervical cancer 25.7%[2].

Data from TULIP Integrated Cancer Clinic Sardjito General Hospital Yogyakarta said that from one year to another, there was an increase in breast cancer cases. In 2005, from 1269 women visiting TULIP, the most case was breast cancer (31.1%) followed by cervical cancer (4.9%) and the most cases were 46 – 50 years old. One study in Yogyakarta showed a transformed trend of age of patient to the younger patient than in western countries accompanied with aggressive phenotypic.

The dominant age group was 40-49 years old compared with that in western countries to be in menopausal ages[2].

Adjuvant combination chemotherapy has been used since 1970 for women with early stage breast cancer subgroup and could decrease the disease mortality[3]. Adjuvant systemic chemotherapy has been addressed for systemic anticancer therapy following primary surgery on early stage breast cancer. Adjuvant chemotherapy on breast cancer has been proven to prolong disease-free and overall survivals despite its potential acute or delayed side effects[5]. Cognitive impairment is one of the delayed side effects of chemotherapy. This side effect is an important issue when considering the productive ages among breast cancer patients particularly in Indonesia.

The etiology of cognitive impairment after chemotherapy has not been well known yet, although some mechanisms had been postulated. Candidate mechanisms were direct neurotoxicity effect (e.g, injuries on neurons of cells around it, change on neurotransmitter level), oxidative stress and DNA impairment, induced hormonal change, immune disregulation and/or cytokine release, and blood clot in small blood vessel of central nervous system (CNS). Some patients could have genetic predisposition to develop cognitive impairment[6,7,8].

Although it is known that cognitive impairment is a complication commonly found among end stage cancer patients, any prove from systemic chemotherapy effect is more suggestive than conclusive. Several studies done did not use prospective longitudinal design, so they could not measure some cognitive function impairment[9]. One suggestion that has been adopted by patients, clinicians, neurophysiologist and other professional health is that breast cancer adjuvant therapy influences cognitive function[10].

Nationally standardized simple measurement tool for detecting mild cognitive impairment is Mini-Mental State examination (MMSE) from Folstein. It is a practical tool that includes some cognitive function domain, such as: memory, executive function, attention, language, praxis, and visuospatial potency. With 30 as the maximal value, patients with mild cognitive or vascular cognitive impairment should have $\geqslant 24$, while a value below 24 is used to differentiate normal and abnormal cognitive function. Since age and educational level also influence MMSE, an examiner should never miss to consider those things before interpreting MMSE result[11,12,13].

Primary objective of this study was to know anthracycline based adjuvant chemotherapy impact on cognitive function of function of breast cancer patients. Secondary objective of this study was to know factors that influence increase or decrease of breast cancer patient's cognitive function receiving anthracycline based adjuvant chemotherapy. Hypothesis of this study is breast cancer patients receiving anthracycline based adjuvant chemotherapy had cognitive function change.

METHOD

This study was a prospective longitudinal study that investigated cognitive function change in breast cancer subjects before, during (3 weeks after 2nd adjuvant chemotherapy), after (3 weeks 4th adjuvant chemotherapy) and 3 months after adjuvant chemotherapy with anthracycline based. Study was done in Internal Medicine Department wards and TULIP cancer outpatient clinic Sardjito General Hospital Yogyakarta. Target population was breast cancer patient receiving anthracycline based adjuvant chemotherapy. Accessible population were breast cancer patients receiving anthracycline based adjuvant chemotherapy being admitted in the Internal Medicine Department wards or TULIP clinic of Dr. Sardjito Yogyakarta.

Inclusion criteria were: women diagnosed as breast cancer from anatomic pathology examination, chemotherapy-naïve, 18-65 years old, stage I-III based on 6th edition American Joint Committee on Cancer (AJCC) TNM classification for breast cancer and include in intermediate-risk or high risk (St Gallen 2007 criteria), performance index with Karnofsky Index > 60%, normal hematological, liver, kidney, and heart function, and agreed to join the study. Exclusion criteria were: illiteracy, pregnant, suffering from another cancer, dementia, had psychiatric impairment, history of head trauma, and history of stroke patients. Based on the calculation of sample number the minimum sample was 34 subjects.

Continue data was presented in mean ± standard deviation (SD) and median (with minimum and maximum range), and categorical data was presented in percentage. On measurement with ordinal scale, Wilcoxon signed rank test for paired

data was used to measure mean differences between first and second, third and fourth measurement, because data was not normally distributed. Multiple linear regressions were used to measure effect of anthracycline based adjuvant chemotherapy to cognitive function change with controlling other independent variables. Statistic evaluation was done with computer software. Statistical significant differences was considered if P<0.05.

RESULT AND DISCUSSION

From October 1st 2008 to October 31st 2009, there were 47 subjects fulfilled inclusion criteria. There were 7 dropped-out subjects due to incomplete chemotherapy. In total, there were 40 subjects finishing the study and analyzed. Subject age mean was 47.08±6.65 with median 8 years old and interval 27-61 years old (table1). This was in accordance with epidemiological data from study in Yogyakarta which showed the age of most breast cancer patients at 40-49 years old[2].

In this study, we observed cognitive function with MMSE of more homogenous sample population, relatively same type of chemotherapy and longer time of observation (interval 180 days from baseline). Iconomou et al. (2004) studied cognitive function using MMSE before and after chemotherapy on 80 solid tumor patients including breast cancer patients undergone chemotherapy. He found MMSE score mean before chemotherapy was 26.89±3.05 (p=0.26), MMSE score <24 was 15% before chemotherapy and 15% after chemotherapy (p=1.0)[9].

Table 1. Baseline Characteristics of the Study Subject

Subject Variable (n=40)	Mean±SD	Median (minimum-maximum)
Age (year)	47.08±6.65	48 (27 – 61)
Educational Level(%)		
- Elementary School	19 (47.5)	
- Junior High School	6 (15.0)	
- Senior High School	8 (20.0)	
- Undergraduate	7 (17.5)	
Body Weight (Kg)	56.63±9.63	56.5 (36.0 – 75.0)
Height (m)	153.35±4.79	154 (142 – 162)
BMI (kg/m2)	24.05±3.74	23.9 (15.79 – 33.78)
Menopausal state (%)		
- Menstrual	23 (57.5)	
- Menopause	17 (42.5)	
Stage (%)		
- IIA	13 (32.5)	
- IIB	9 (22.5)	
- IIIA	9 (22.5)	
- IIIB	9 (22.5)	
Chemotherapy regiment (%)		
- AC	35 (87.5)	
- EC	5 (12.5)	
Histopatology (%)		
- Ductal Carcinoma	38 (95.0)	
- Papillary Carcinoma	2 (5.0)	
Comorbid (%)		
- None	34 (85.0)	
- Hypertension	4 (10.0)	
- Diabetic	2 (5.0)	
MMSE score	29.28±1.20	30 (26 – 30)

BMI = Body Mass Index, AC = *adriamycin + cyclophosphamide, EC = Epirubicin + cyclophosphamide, MMSE = Mini Mental State Examination, SD = Standard Deviation*

On table 2, 3 and 4 there were MMSE score decrease on week 3 after 2nd adjuvant chemotherapy, 3 weeks after 4th adjuvant chemotherapy and 3 months after 4th adjuvant chemotherapy compared with prior to anthracycline based adjuvant chemotherapy. These decreases were statistically significant ($p<0.001$). From five MMSE sub scores, there were some statistically significant decreases ($p<0.05$) on attention and calculation, memory, and language functions in compare with prior to chemotherapy, while orientation function only decreased significantly on 3 weeks ($p=0.014$) and 3 months ($p=0.004$) after 4th adjuvant chemotherapy.

Table 2. MMSE score mean difference 3 weeks after 2nd adjuvant chemotherapy

Measurement	T_0 (Mean±SD)	T_1 (Mean±SD)	$\Delta T_0 - T_1$ (Mean±SD)	*P* value
Orientation	9.88±0.34	9.83±0.45	0.05±0.22	0.157*
Registration	3.00±0.00	3.00±0.00	0.00±0.00	1.0*
Attention&Calculation	4.83±0.39	4.63±0.71	0.20±0.46	0.011*
Memory	2.93±0.27	2.68±0.47	0.25±0.49	0.004*
Language	8.68±0.62	8.48±0.75	0.20±0.41	0.005*
MMSE Score	29.28±1.20	28.60±1.69	0.68±0.80	<0.001*

T_0 = before chemotherapy, T_1 = 3 weeks after 2nd adjuvant chemotherapy, SD = Standard Deviation, MMSE = *Mini Mental State Examination, * Wilcoxon-signed rank test*

Table 3. MMSE score mean difference 3 weeks after 4th adjuvant chemotherapy

Measurement	T_0 (Mean±SD)	T_1 (Mean±SD)	$\Delta T_0 - T_1$ (Mean±SD)	*P* value
Orientation	9.88±0.34 0	9.65±0.7	0.23±0.53	0.014*
Registration	3.00±0.00	3.00±0.00	0.00±0.00	1.0*
Attention&Calculation	4.83±0.39	4.43±0.78	0.40±0.55	<0.001*
Memory	2.93±0.27	2.68±0.53	0.25±0.49	0.004*
Language	8.68±0.62	8.43±0.75	0.25±0.59	0.012*
MMSE Score	29.28±1.20	28.18±1.89	1.10±1.06	<0.001*

T_0 = before chemotherapy, T_1 = 3 weeks after IV adjuvant chemotherapy, SD = Standard Deviation, MMSE = *Mini Mental State Examination, * Wilcoxon-signed rank test*

Table 4. MMSE score mean difference 3 months after 4th adjuvant chemotherapy

Measurement	T_0 (Mean±SD)	T_1 (Mean±SD)	$\Delta T_0 - T_1$ (Mean±SD)	*P* value
Orientation	9.88±0.34	9.63±0.63	0.25±0.49	0.004*
Registration	3.00±0.00	3.00±0,00	0.00±0.00	1.0*
Attention&Calculation	4.83±0.39	4.38±0.87	0.45±0.68	0.001*
Memory	2.93±0.27	2.58±0.59	0.35±0.58	0.001*
Language	8.68±0.62	8.28±0.85	0.40±0.67	0.001*
MMSE Score	29.28±1.20	27.85±2.03	1.43±1.36	<0.001*

T_0 = *before chemotherapy,* T_1 = 3 months after 4th adjuvant *chemotherapy, SD = Standard Deviation, MMSE = Mini Mental State Examination, * Wilcoxon-signed rank test*

Wefel et al. (2004) did a prospective longitudinal study on 18 breast cancer patients before, during, 6 months after (>3weeks after) and 18 months after chemotherapy. Before chemotherapy, 33% patients had cognitive impairments, 6 months later 60% patients had cognitive decrease on at least one domain. However, there were improvement (although still under baseline) in 50% patients with decreased cognitive in 18 months after 4th adjuvant chemotherapy, but not in other 50% [14].

Using traditional cut off point for MMSE which is <24, 2.5% cognitive impairment was found in 3 months after 4th adjuvant chemotherapy, although not statistically significant (p=1.0) (table 5), which was different from prior study by Tchen et al. (2003) which was 16%. This could happen probably because MMSE was less sensitive to detect cognitive impairment on breast cancer patients who received chemotherapy. Another possibility was that MMSE measurement was done before manifestation of chemotherapy effect, and this study was not designed to measure late effect of chemotherapy.

Table 5. Change of MMSE score and cognitive impairment

Score	T_0	T_1	T_2	T_3	*P* value
MMSE	29.28±1.20	28.60±1.69	28.18±1.89	27.85±2.03	<0.001[¥]
Decrease ≥ 3	-	1(2.5%)	4(10%)	7(17.5%)	0.057*
Score<24	0(0%)	0(0%)	0(0%)	1(2.5%)	1.0*

T_0 = before chemotherapy, T_1 = 3 weeks after II 2nd adjuvant chemotherapy, T_2 = 3 weeks after 4th adjuvant chemotherapy, T_3 = 3 months after 4th adjuvant chemotherapy, MMSE = *Mini Mental State Examination, ¥Friedman-test, *Fisher-exact-test*

In this study (table 5) there was statistically significant MMSE score decrease on 3 months after 4th adjuvant chemotherapy in compare with prior to chemotherapy (p<0.001). Decrease of 3 points or more of MMSE which need evaluation for cognitive impairment was 2.5% on 3 weeks after 2nd adjuvant chemotherapy and 17.5% on 3 months after 4th adjuvant chemotherapy, showed relationship between amount of chemotherapy cycle (dose intensity and cumulative dose) received by patients and increased of cognitive function impairment. Beside that, the longer MMSE score measurement done after chemotherapy, the higher cognitive function decrease.

Study by Ahles et al. (2002) found a relationship of cognitive impairment and chemotherapy cycle received. Chemotherapy regiment gave influence to cognitive impairment and some drug had higher neurotoxicity effect. Probability of cognitive impairment after cyclophosphamide, methorexate and 5-fluorouracyl (CMF) was higher than anthracycline[7,16]. Anthracycline based chemotherapy toxicity depends on dosage (dose intensity and cumulative dose) beside the type of anthracycline used[17]. This study used anthracycline based chemotherapy as recommended by St. Galen 2007 [18], in which anthracycline regiment (AC/EC) had less neurotoxicity than prior regiment (CMF). This may cause a non-significant cognitive impairment.

Table 6. Side effect during chemotherapy

Side Effect Chemotherapy	T_0-T_1 N (%)	T_1-T_2 N (%)	T_0-T_2 N (%)
Anemia (Hb<12 g/dl)	18 (45)	24 (60)	27 (67.5)
Neutropenia (ANC<10^3/µL)	8 (20)	13 (32)	18 (45)

T_0 = before chemotherapy, T_1 = 3 weeks after 2nd adjuvant chemotherapy, T_2 = 3 weeks after 4th adjuvant chemotherapy, ANC = *Absolute Neurotrophyl Count.*

Hematological toxicity degree 3 or 4 according to NCI presented as neutropenia (ANC $<10^3/mm^3$) occurred in 8 (20%) subjects after 2nd/3rd chemotherapy. This side effect increased in 13 (32%) subject after 4th/6th chemotherapy. Total number of patient experienced neutropenia before chemotherapy until 3 weeks after 4th chemotherapy were 18 (45%) subjects. When we used the criteria from NCI for 3rd and 4th degree anemia (Hb < 8g/dl), we did not find any case affected by chemotherapy. However, when we use WHO/NCI criteria (Hb < 12 g/dl) we found 18 (45%) subjects suffered from anemia after 2nd/3rd chemotherapy. This number increased to be 24 (60%) after 4th/6th chemotherapy with total 27 (67.5%) from 1st to 4th/6th chemotherapy.

Table 7. MMSE score mean change difference toward independent variable

Variable	N (%)	ΔT_0- T_3 (Mean±SD)	*P* value
Subject Age			0,171*
- <50 years old	25 (62.5)	1.68±1.46	
- ≥ 50 years old	15 (37.5)	1.00±1.07	
Educational Level			0,001#
- Elementary School	19 (47.5)	2.11±1.29	
- Junior High School	6 (15.0) 1.83±0.98		
- Senior High School	8 (20.0) 0.63±0.92		
- Undergraduate	7 (17.5) 0.14±0.90		
Menopausal state			0.374*
- Menstrual	23 (57.5)	1.52±1.20	
- Menopause	17 (42.5)	1.29±1.57	
Stage of Breast Cancer			0.047*
- II	22 (55.0)	1.00±0.98	
- III	18 (45.0)	1.94±1.59	
BMI Classification			0.550#
- Underweight	2 (5.0)	1.50±0.71	
- Normal	16 (40.0)	1.56±0.96	
- Overweight/Obese	22 (55.0)	1.32±1.64	
Neutropenia side effect			0.433*
- ANC < 10^3 /µL	18 (45.0)	1.17±1.10	
- ANC ≥ 10^3/µL	22 (55.0)	1.64±1.53	
Anemia side effect			0.475*
- Hb < 12 g/dl	27 (67.5)	1.37±1.47	
- Hb ≥ 12 g/dl	13 (32.5)	1.54±1.13	

T_0 = before chemotherapy, T_3 = 3 months after 4th adjuvant chemotherapy, ANC = *Absolute Neurotrophyl Count*, MMSE = *Mini Mental State Examination*, SD = *Standard Deviation, *Mann-Whitney-U-test, #Kruskal-Wallis-test.*

In this study, there was MMSE score mean change which was statistically significant by univariate analysis on two independent variable (table 7), which were educational level and breast cancer stage. Table 8 showed statistically significant difference when multivariate analysis with linear regression was used to the variables.

Post-menopausal women reported significant greater memory impairment than pre-menopausal women. Adjuvant chemotherapy itself caused ovary failure on almost 77% pre-menopausal women with breast cancer. On healthy women, ovary failure caused lost of estrogen and progesterone secretion and related to deficit in

attention, learning, and memory[19]. In this study, there was no significant mean MMSE score change based on age or menopausal status (table 7).

In this study (table 7), there was a significant MMSE score mean decrease on stage II in compare with stage III breast cancer patients. This might happen due to disease progressivity as indirect factor, beside anti-neoplastic therapy which had contribution on cancer patient cognitive deficit[19,20].

Anemia was a common side effect of cancer and/or chemotherapy which could cause fatigue and brain oxygenation decrease. Jacobsen reported that patient with worse anemia level showed worse memory visual image and executive function than patient with normal hemoglobin or mild anemia. This effect had relationship with fatigue. This mechanism could cause acute cognitive impairment but less possible causing cognitive impairment when hemoglobin level improved to normal[7]. In this study anemia did not significantly influence decrease of MMSE score (table 7). This may be because the anemia was a mild anemia (hemoglobin level 9.0-11.0g/dl).

Beside that, side effect during other chemotherapy also did not significantly influence MMSE score decrease (table 7). This may be due to no incidence of febrile neutropenia during or after chemotherapy. Febrile and infection were also indirect factors which had contribution on cancer patient cognitive impairment beside antineoplastic therapy[19,20].

Table 8 showed that on multivariate analysis, educational level had the greatest influence on MMSE score decrease, with $p < 0.001$ (95% CI: -0.926- -0.308). It means that breast cancer patients receiving anthracycline based adjuvant chemotherapy with lower educational level has more significant MMSE score decrease than breast caner patient with higher educational state. This study was in line with study which said that education could give more protection on neuron degradation or delayed dementia onset. Education could improvise neuron to do the functional task of other dying neuron. Brain will degenerate faster when rarely used. Education could also increase brain memory by increasing neuro-cortical synaps density[21].

Table 8. Linear Regression between MMSE score change (ΔT_{0}-T_{3}) and educational state and stage of cancer

Variable	B	SE	β	t	*P* value	95% IC
Constanta	1.909	0.700		2.727	0.010	0.491– 3.328
Education	-0.617	0.153	-0.539	-4.044	<0.001	-0.926 - -0.308
Stage	0.549	0.359	0.204	1.529	0.135	-0.178 – 1.276

T_0 = before chemotherapy, T_3 = 3 months after 4th adjuvant chemotherapy, B = β estimation, SE = Standard Error, CI = Confidence Interval, MMSE = *Mini Mental State Examination*

There were some limitations in this study. First, depression and anxiety were not measured in this study because the author did not have objective parameters to measure depression and anxiety. Second, this study design was a pre-post- analysis study without control group, so effect of exposure to outcome could not certainly be defined. Third, patients did not visit as scheduled and limited time of observation.

CONCLUSION

In this study, there was a significant decrease on MMSE score of breast cancer patient receiving anthracycline based adjuvant chemotherapy on 3 weeks after 2nd adjuvant chemotherapy, 3 weeks after 4th adjuvant chemotherapy and after 3 months after 4th adjuvant chemotherapy in compare with prior to chemotherapy.

SUGGESTION

Cognitive function evaluation of breast cancer patients receiving adjuvant chemotherapy is needed. It is needed especially for chemotherapy that contains neurotoxicity agent, to improve patients' quality of life.

REFERENCES

1. Ahles T.A., Saykin A.J., Furstenberg, C.T. 2002. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol, 20(2): 485 – 93.
2. Ahles, T.A. & Saykin, A.J. 2007. Candidate mechanisms for chemotherapy-induced cognitive changes. Nature Reviews Cancer, 7: 192 – 201.
3. Aryandono T. 2008. Kemajuan dalam Penelitian, Penanganan, dan Deteksi Dini Penderita Kanker Payudara dengan Perhatian Khusus pada Kualitas Hidup. Pidato Pengukuhan Guru Besar Fakultas Kedokteran UGM.
4. Bender, C.M., Paraska, K.K., Sereika, S.M., Ryan, C.M., Berga, S.L. 2001. Cognitive Function and Reproductive Hormones in Adjuvant Therapy for Breast Cancer: A Critical Review. J Pain Symptom Manage 21(5): 407 – 24
5. Brezden, C.B., Phillips, K.A., Abdolell, M., Bunston, T., Tannock, I.F. 2000. Cognitive Function in Breast Cancer Patients Receiving Adjuvant Chemotherapy. J Clin Oncol, 18: 2695 – 701.
6. Colozza, M., Azambuja, E.D., Cardoso, F., Bernard, C., Piccart, M.J. 2006. Breast Cancer: Achievements in Adjuvant Systemic Therapies in the Pre-Genomic Era. The Oncologist, 11: 111 – 25.
7. Dahlan, P. 1999. Pemeriksaan Neuropsikologi Pada Demensia. B NeuroSains, 1(1): 17 – 23.
8. DeSantis, C., Siegel, R., Jemal, A. 2007. Breast Cancer Facts & Figures 2007-2008. Am Cancer Society, 1 – 32.
9. Fan, H.G.M., Tchen, N.H., Yi, Q.L., Chemerynsky, I., Downie, F.P., Sabate, K., Tannock, I.F. 2005. Fatigue, Menopausal Symptoms, and Cognitive Function in Women After Adjuvant Chemotherapy for Breast Cancer: 1- and 2-Year Follow-Up of a Prospective Controlled Study. J Clin Oncol, 23: 8025 – 32.
10. Goldhirsch, A., Glick, J.H., Gelber, R.D., Coates, A.S., Thurlimann, B., Senn, H.J., & Panel Members. 2005. Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005. Ann Oncol, 16: 1569 – 83.
11. Harbeck, N. & Jakesz, R. 2007. St Gallen 2007: Breast Cancer Treatment Consensus Report. Breast Care, 2: 130 – 4.
12. Hayes, D.F. 2007. Adjuvant systemic therapy for early breast cancer: Rationale, assessing the need for and benefit from therapy, and treatment guidelines. Up To Date® 15.3.
13. Iconomou, G., Mega, V., Koutras, A., Iconomou, A.V., Kalofonos, H.P. 2004. Prospective Assesment of Emosional Distress, Cognitive Function, and Quality of Life in Patients with Cancer Treated with Chemotherapy. Cancer, 101: 404 – 11.
14. Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., Bishop, H., Hodson, N., Mitra, S., Sadler, G., Shah, E., Stein, R., Whitehead, S., Winstanley, J. 2006. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer, 94: 828 – 34.
15. Lwanga, S.K. & Lemeshow, S. 1991. Two sample situations. In: S.K. Lwanga & S. Lemeshow. Sample size determination in health studies. A practical manual: 6 – 8. Geneva: WHO.
16. Matsuda, T., Takayama, T., Tashiro, M., Nakamura, Y., Ohashi, Y., Shimozuma, K. 2005. Mild Cognitive Impairment after Adjuvant Chemotherapy in Breast Cancer Patients – Evaluation of Appropriate Research Design and Methodology to Measure Symptoms. Breast Cancer, 12: 279 – 87.
17. Minotti, G., Menna, P., Salvatorelli, E., Cairo G., Gianni, L. 2004. Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity. Pharmacol Rev, 56(2): 186 – 229.
18. National Cancer Institute (NCI). 2003. Appendix 4 NCI Common Toxicity Criteria (CTC) Version 3.0.
19. Orrell, M. & Sahakian, B. 1995. Education and dementia. Br Med J, 310: 951 – 2.
20. O'Shaughnessy, J. 2003. Chemotherapy-Related Cognitive Dysfunction in Breast Cancer. Semin Oncol Nurs, 19(4): 17 – 24.
21. Pasaribu, B.O. 2005. Parameter Biokimia Untuk Mild Cognitive Impairment (MCI) dan Alzheimer. Forum Diagnosticum, 2: 1 – 7.
22. Perneczky, R., Wagenpfeil, Kornossa, K., Grimmer, T., Diehl, J., Kurz, A. 2006. Mapping Scores Onto Stages : MMSE and Clinical Dementia Rating (abstract). Am J Geriatr Psychiatry, 14(2): 139 – 44.
23. Petersen, R.C., Stevens, J.C., Ganguli, M., Tangalos, Cummings & DeKosky. 2001. Practice Parameter : Early Detection of Dementia: Mild Cognitive Impairment (An Evidence Based Review). Report of the Quality Standards Subcommittee of the America Academy of Neurology. Neur, 56: 1133 – 42.

24. Phillips, K.A. & Bernhard, J. 2003. Adjuvant Breast Cancer Treatment and Cognitive Function: Current Knowledge and Research Directions. J Natl Cancer Inst, 95: 190 – 7.
25. Rodgers, G.M., Becker, P.S., Bennett, C.L. 2008. Cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw, 6: 536.
26. Setyopranoto, I. & Lamsudin, R. 1999. Kesepakatan Penilaian Mini Mental State Examination (MMSE) Pada Penderita Stroke Iskemik Akut di RSUP Dr. Sardjito Yogyakarta. B NeuroSains, 1(1): 73 – 6.
27. Shapiro, C. 2007. Side effects of adjuvant chemotherapy for early stage breast cancer. Up To Date® 15.3.
28. Shadlen, M.F. & Larson, E.B. 2007. Evaluation of cognitive impairment and dementia. Up To Date® 15.3.
29. Singletary, S.E. & Connolly, J.L. 2006. Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual. CA Cancer J Clin, 56: 37 – 47.
30. Soejono, C.H., Harimurti, K., Setiati, S., Damping, C.E. 2006. Pedoman Diagnosis dan Tatalaksana MCI dan VCI, dalam Konsensus Nasional-Peran Dokter Spesialis Penyakit Dalam Untuk Deteksi Dini, Diagnosis Dan Penatalaksanaan Gangguan Kognitif Ringan Pada Usia Lanjut. Perhimpunan Gerontologi Medik Indonesia. Jakarta: 1 – 28. 56
31. Tannock, I.F., Ahles, T.A., Ganz, P.A., van Dam, F.S. 2004. Cognitive Impairment Associated With Chemotherapy for Cancer: Report of a Workshop. J Clin Oncol, 22: 2233 – 39.
32. Tchen, N., Juffs, H.G., Downie, F.P. 2003. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J Clin Oncol, 21: 4175 – 83.
33. Vardy, J. & Tannock, I. 2007. Cognitive function after chemotherapy in adults with solid tumours. Crit Rev Oncol/Hematol, 63: 183 – 202.
34. Vardy, J., Wefel, J.S., Ahles, T., Tannock, I.F., Schagen, S.B. 2008. Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann Oncol, 19: 623 – 29.
35. Visser, P.J. 2006. Mild Cognitive Impairment. Dalam Pathy, M.S., Sinclair, J., & Morley, J.E. (Eds) Principles and Practice of Geriatric Medicine 4th (ed). John Wiley and Sons. Ltd: 1 – 7.
36. Wefel J.S., Lenzi R., Theriault R.L., Davis R.N., Meyers C.A. 2004. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer, 100(11): 2292 – 9.
37. World Health Organization. 2000. The Asia-Pacific perspective: redefining obesity and its treatment. World Health Organization. Melbourne.
\38. Wright, J.D. 2007. Mild Cognitive Impairment. Up To Date® 15.3.